Peptides compounds for delivering active agents across the blood-brain barrier

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Inventor: LEONE-BAY ANDREA; HO KOC-KAN; LEIPOLD HARRY R; MILSTEIN SAM J; GSCHNEIDNER DAVID; SARUBBI DONALD J; WANG ERIC

Applicant: EMISHERE TECHNOLOGIES INC

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- International: C07C233/83

- european:

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Abstract of **NZ507275**

A composition or salt thereof is described comprising: at least one active agent, and a compound, 8(N-2-Hydroxy-4-methoxybenzoyl) aminocaprylic acid (as shown). The biologically active agent could be interferon, interleukin-1, interleukin-II, insulin, heparin, calcitonin, oxytocin, vasopressin, vancomycin, desferrioxamine, parathyroid hormone, or any combination thereof. This composition is to be passed across a mammalian blood/brain barrier.

NZ 507275 - s13 Citation.

1946/2C892

COMPOUNDS AND COMPOSITIONS FOR DELIVERING ACTIVE AGENTS

FIELD OF THE INVENTION

The present invention relates to compounds for delivering active agents, and particularly biologically or chemically active agents. These compounds are used as carriers to facilitate the delivery of a cargo to a target. The carrier compounds are well suited to form non-covalent mixtures with biologically-active agents for oral administration to animals. Methods for the preparation and administration of such compositions are also disclosed.

BACKGROUND OF THE INVENTION

Conventional means for delivering active agents are often severely limited by biological, chemical, and physical barriers. Typically, these barriers are imposed by the environment through which delivery occurs, the environment of the target for delivery, or the target itself. Biologically or chemically active agents are particularly vulnerable to such barriers.

For example in the delivery to animals of biologically active or chemically active pharmacological and therapeutic agents, barriers are imposed by the body. Examples of physical barriers are the skin and various organ membranes that must be traversed before reaching a target. Chemical

barriers include, but are not limited to, pH variations, lipid bi-layers, and degrading enzymes.

These barriers are of particular significance in the design of oral delivery systems. Oral delivery of many biologically or chemically active agents would be the route of choice for administration to animals if not for biological, chemical, and physical barriers such as varying pH in the gastro-intestinal (GI) tract, powerful digestive enzymes, and active agent impermeable gastro-intestinal membranes. Among the numerous agents which are not typically amenable to oral administration are biologically or chemically active peptides, such as calcitonin and insulin; polysaccharides, and in particular mucopolysaccharides including, but not limited to, heparin; heparinoids; antibiotics; and other organic substances. These agents are rapidly rendered ineffective or are destroyed in the gastro-intestinal tract by acid hydrolysis, enzymes, or the like.

Earlier methods for orally administering vulnerable pharmacological agents have relied on the co-administration of adjuvants (e.g., resorcinols and non-ionic surfactants such as polyoxyethylene oleyl ether and n-hexadecylpolyethylene ether) to increase artificially the permeability of the intestinal walls, as well as the co-administration of enzymatic inhibitors (e.g., pancreatic trypsin inhibitors, diisopropylfluorophosphate (DFF) and trasylol) to inhibit enzymatic degradation.

Liposomes have also been described as drug delivery systems for insulin and heparin. See, for example, U.S. Patent No. 4,239,754; Patel et al. (1976), *FEBS Letters*, Vol. 62, pg. 60; and Hashimoto et al. (1979), *Endocrinology Japan*, Vol. 26, pg. 337.

However, broad spectrum use of such drug delivery systems is precluded because: (1) the systems require toxic amounts of adjuvants or inhibitors; (2) suitable low molecular weight cargos, i.e. active agents, are not

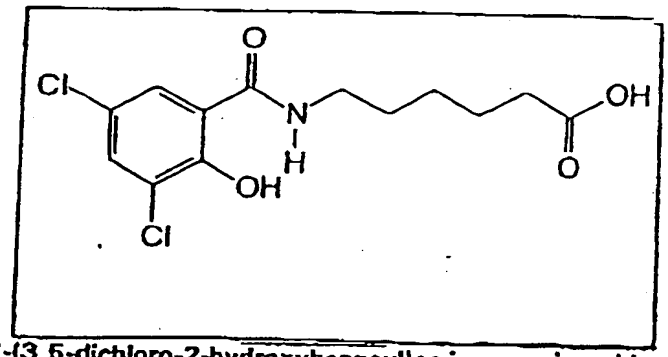
available; (3) the systems exhibit poor stability and inadequate shelf life; (4) the systems are difficult to manufacture; (5) the systems fail to protect the active agent (cargo); (6) the systems adversely alter the active agent; or (7) the systems fail to allow or promote absorption of the active agent.

More recently, microspheres of artificial polymers of mixed amino acids (proteinoids) have been used to deliver pharmaceuticals. For example, U.S. Patent No. 4,925,673 describes drug-containing proteinoid microsphere carriers as well as methods for their preparation and use. These proteinoid microspheres are useful for the delivery of a number of active agents.

There is still a need in the art for simple, inexpensive delivery systems which are easily prepared and which can deliver a broad range of active agents.

SUMMARY OF THE INVENTION

Compounds and compositions which are useful in the delivery of active agents are provided. These compositions include at least one active agent, preferably a biologically or chemically active agent, and at least one of the following compounds 1-193, or salts thereof.



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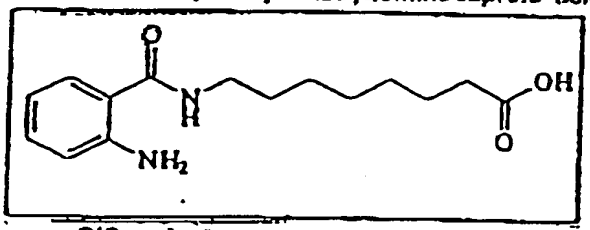
6-N-(3,5-dichloro-2-hydroxybenzoyl)aminocaproic acid



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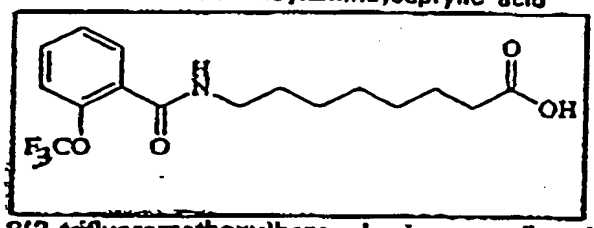
8(2-aminobenzoylamino)caprylic acid



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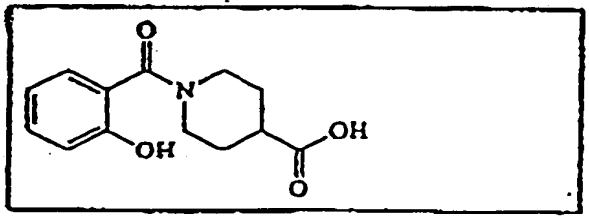
8(2-trifluoromethoxy)benzoylamino caprylic acid



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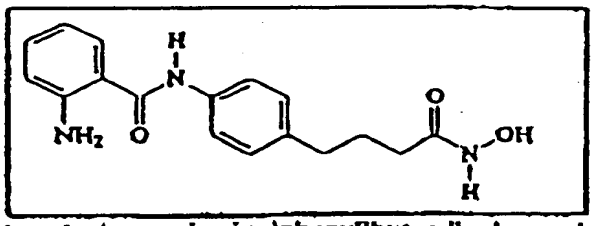
N-(2-hydroxybenzoyl)isonipecotic acid



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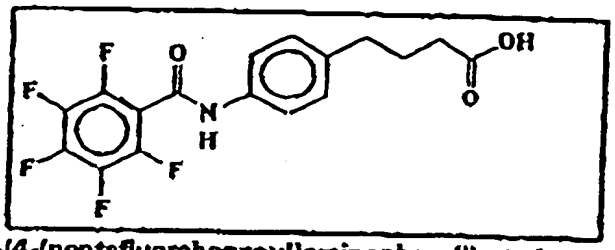
4-[4-(2-aminobenzoylamino)phenyl]butyrylhydroxamic acid



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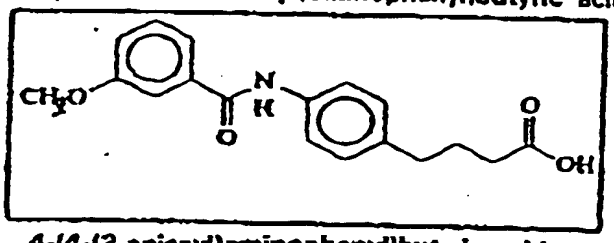

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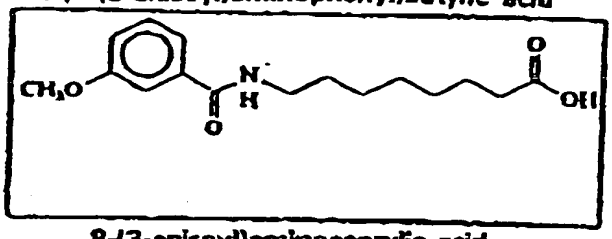
4-(4-(3-anisoyl)aminophenyl)butyric acid



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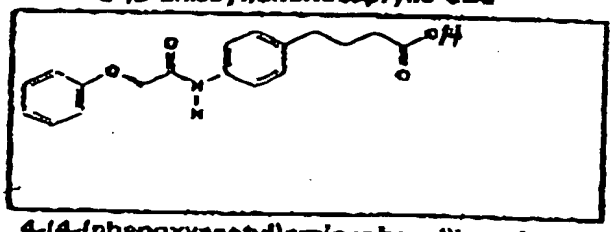
8-(3-anisoyl)aminocaprylic acid



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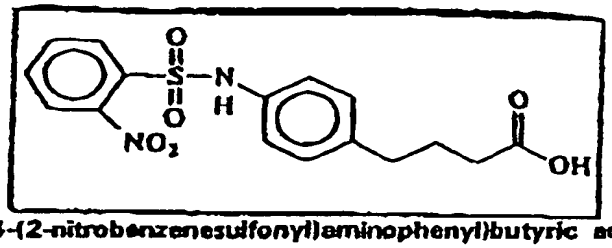
4-(4-(phenoxyacetyl)aminophenyl)butyric acid



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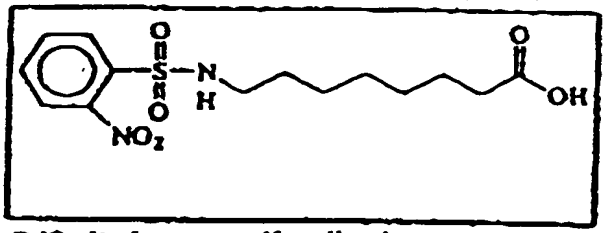
4-(4-(2-nitrobenzenesulfonyl)aminophenyl)butyric acid



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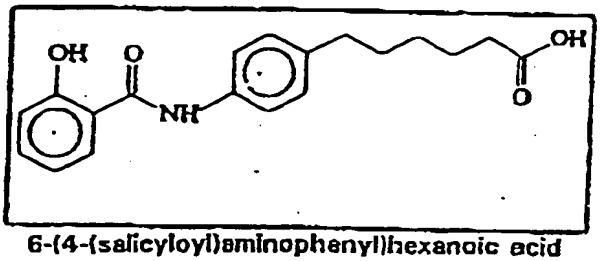
8-(2-nitrobenzenesulfonyl)aminocaprylic acid



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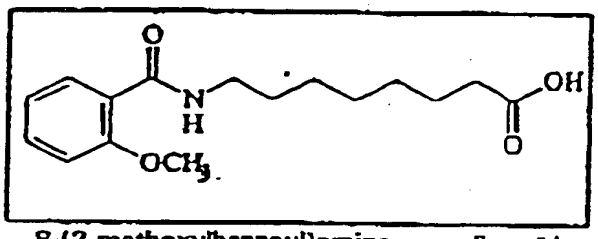
6-(4-(salicyloyl)aminophenyl)hexanoic acid



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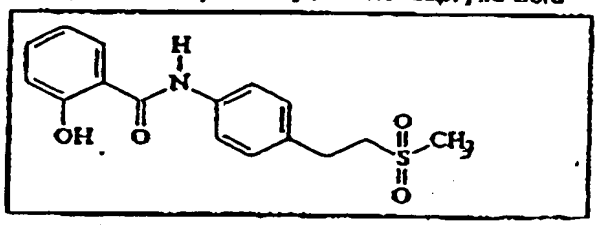
8-(2-methoxylbenzoyl)amino caprylic acid



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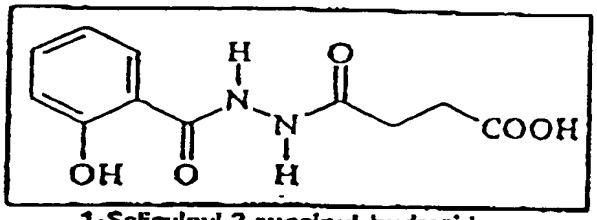
2-[(4-salicyloyl)aminophenyl]ethyl methyl sulfone



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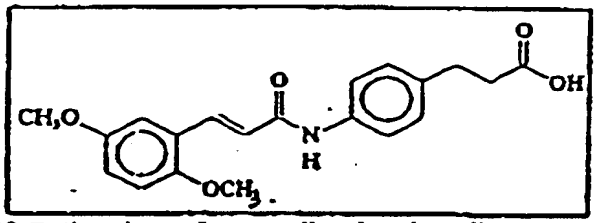
1-Salicyloyl-2-succinyl hydrazide



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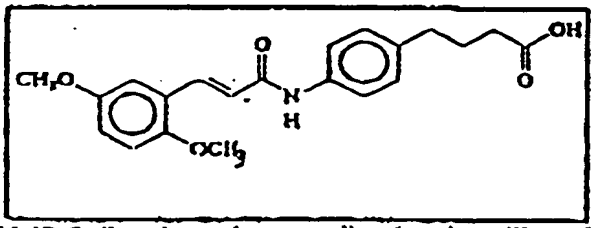
3-(4-(2,5-dimethoxycinnamoyl)aminophenyl)propionic acid



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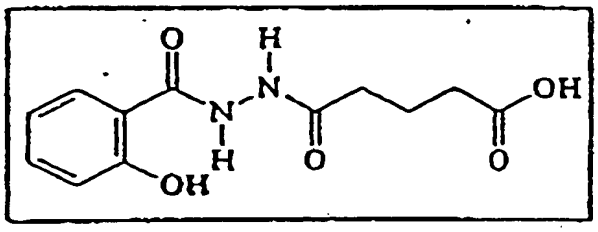

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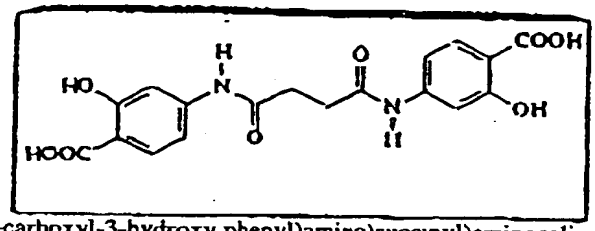
1-salicyloyl-2-glutaryl hydrazide



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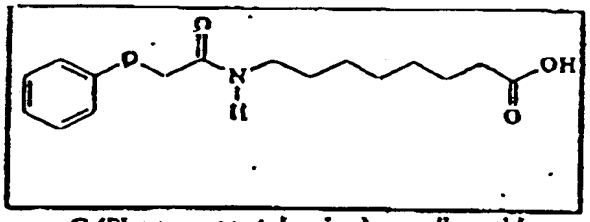
4-(4-((4-carboxyl-3-hydroxy phenyl)amino)succinyl)aminosalicyclic acid



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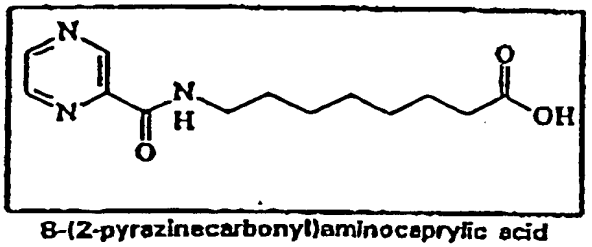
8-(Phenoxyacetylamino)caprylic acid



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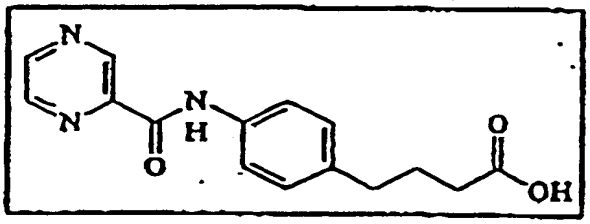
8-(2-pyrazinecarbonyl)aminocaprylic acid



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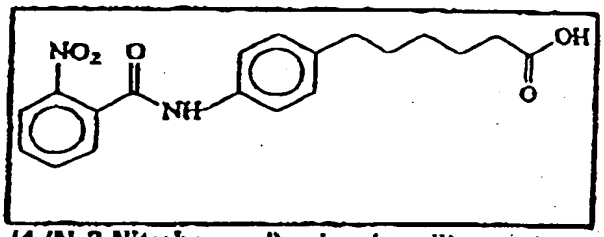

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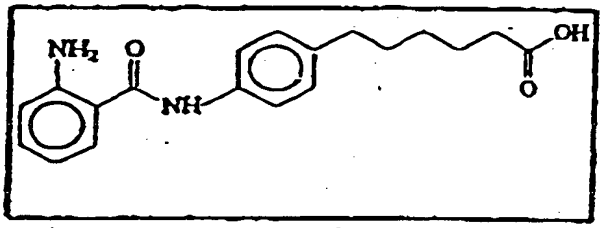
6-(4-(N-2-Nitrobenzoyl)aminophenyl)hexanoic acid



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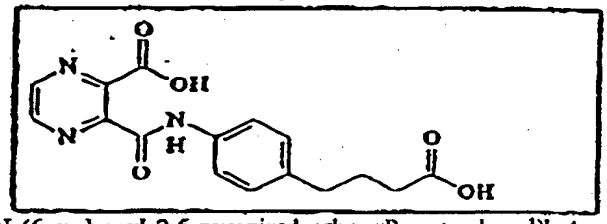

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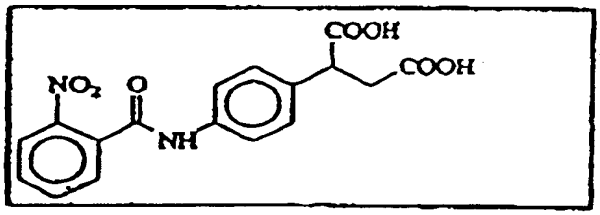
4-(4-(N-(6-carboxyl-2,5-pyrazinylcarboxyl)aminophenyl)butyric acid



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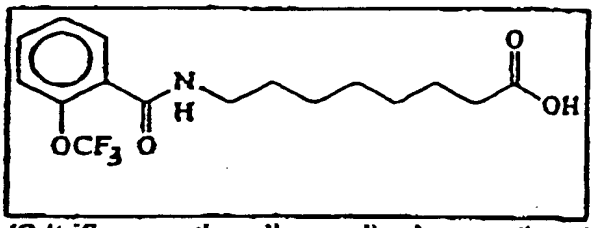
4(2-Nitrobenzoyl)aminophenylsuccinic acid



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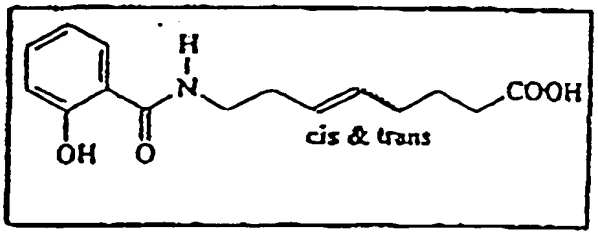

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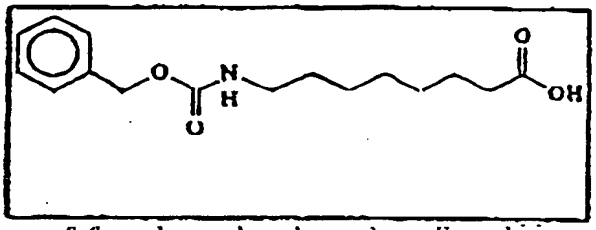

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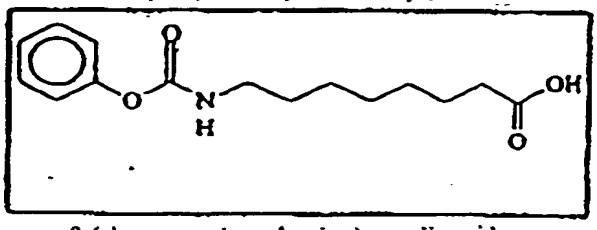
8-(benzyloxycarbonylamino)caprylic acid



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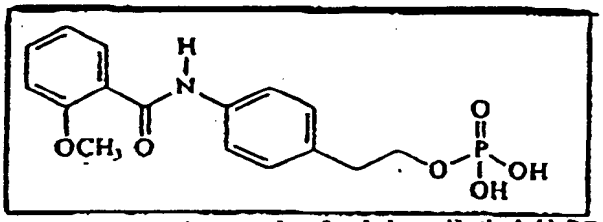

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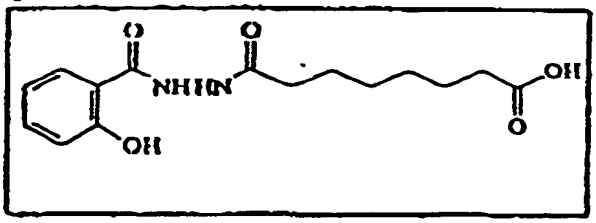
2-[4-(2-Methoxybenzoylamino)phenyl]ethyl H_2PO_4



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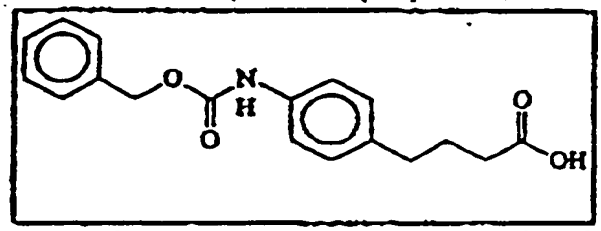
1-salicyloyl-2-suberyl hydrazide



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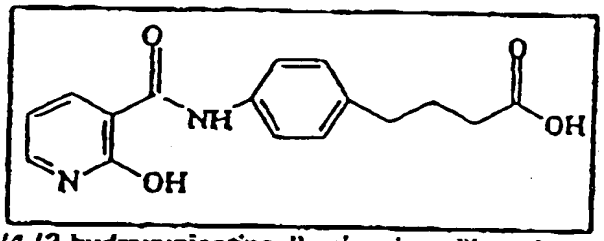
4-(4-benzyloxycarbonylaminophenyl)butyric acid



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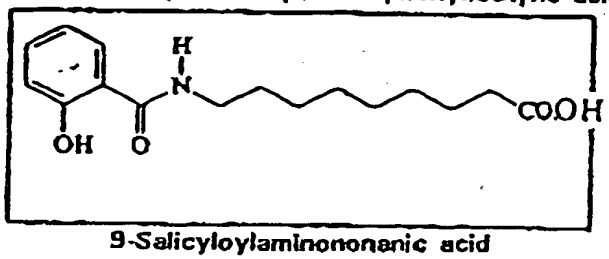

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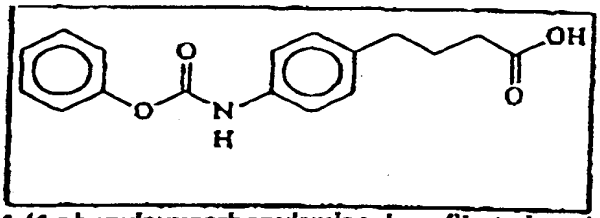
9-Salicyloylaminononanic acid



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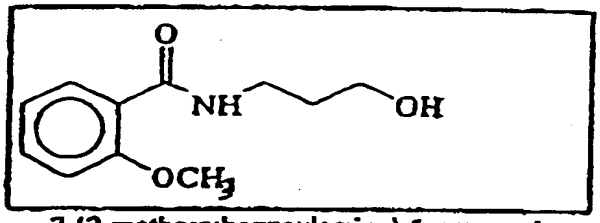
4-(4-phenyloxycarbonylaminophenyl)butyric acid



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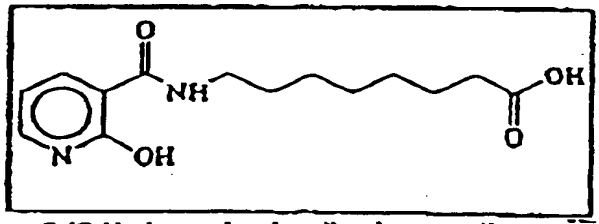
3-(2-methoxybenzoylamino)-1-propanol



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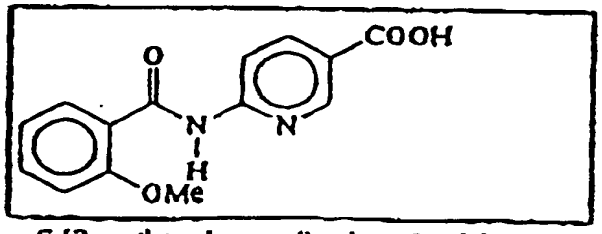
8-(2-Hydroxynicotinoyl)aminocaprylic acid



39

6-(2-methoxybenzoyl)amino nicotinic acid

WHAT WE CLAIM IS:

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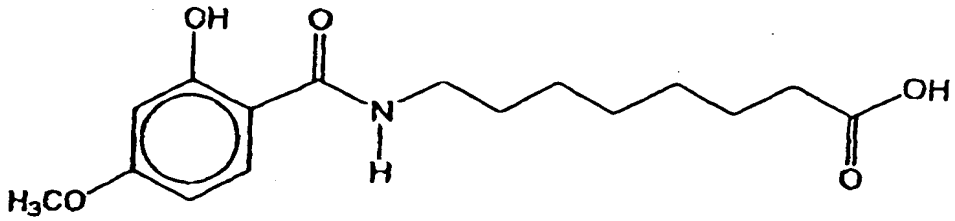
1. A composition comprising:

(A) at least one active agent; and

(B) a compound having the formula



or a salt thereof.

2. The composition of claim 1, wherein the active agent is selected from the group consisting of biologically active agents, chemically active agents, and any combination thereof.

3. The composition of claim 2, wherein the biologically active agent comprises at least one peptide, mucopolysaccharide, carbohydrate, or lipid.

4. The composition of claim 2, wherein the biologically active agent is selected from the group consisting of human growth hormones, bovine growth hormones, growth hormone-releasing hormones, interferons, interleukin-1, interleukin-II, insulin, heparin, low molecular weight heparin, calcitonin, erythropoietin, atrial naturetic factor, antigens, monoclonal antibodies, somatostatin, adrenocorticotropin, gonadrotropin releasing hormone, oxytocin, vasopressin, cromolyn sodium, vancomycin, desferrioxamine, parathyroid hormone, and any combination thereof.

5. The composition of claim 4, wherein the biologically active agent comprises interferon, interleukin-1, interleukin-II, insulin, heparin, low molecular weight heparin calcitonin, oxytocin, vasopressin, vancomycin, desferrioxamine, parathyroid hormone, any combination thereof.

6. The composition of claim 5, wherein said biologically active agent comprises parathyroid hormone.

7. A dosage unit form comprising

(A) the composition of any of claims 1 to 6; and

(B) (a) an excipient,

(b) a diluent,

(c) a disintegrant,

(d) a lubricant,

(e) a plasticizer,

(f) a colorant,

(g) a dose vehicle, or

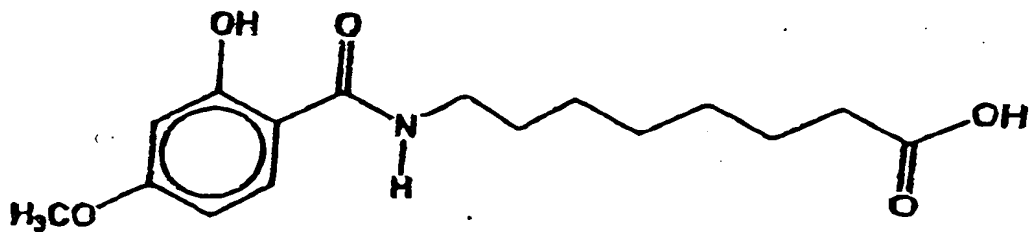
(h) any combination thereof.

8. The dosage unit form of claim 7, comprising a tablet, a capsule, or a liquid.

9. The dosage unit form of any of claims 7 and 8, wherein a dosing vehicle is selected from the group consisting of water, 1,2-propane diol, ethanol, and any combination thereof.

10. A method for administering a biologically-active agent to an animal, said method comprising administering orally, intranasally, sublingually, intraduodenally, subcutaneously, rectally, vaginally, bucally or ophthalmically to said animal the composition of any of claims 1 to 6, wherein said method is not for medical treatment of humans.

11. A compound having the formula



or a salt thereof.

12. A method for preparing a composition, said method comprising mixing:

(A) at least one active agent;

(B) the compound of claim 11; and

(C) optionally, a dosing vehicle.

13. A method for passing a biologically active agent across the blood/brain barrier of an animal, said method comprising administering to said animal the composition of any claims 1 to 6, wherein said method is not for medical treatment of humans.

End of claims

-JPL

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